Remarks:

Claim 8 has been amended to add a comma after the word "vagina," as suggested by the Office. Claims 1-10 remain in the application.

The §112, First Paragraph, Rejections

Claims 1, 4, and 6-10.

Claims 1, 4, and 6-10 were rejected under 35 U.S.C. §112, first paragraph, as having an inadequate written description. In particular, the Office found an insufficient description for the functional term "a bFGF-active PAF antagonist."

The MPEP §2163 (pg. 2100-163) states that "[t]here is a strong presumption that an adequate written description of the claimed invention is present in the specification as filed." In the same paragraph, the MPEP states that "rejection of an original claim for lack of written description should be rare." The Claims in the instant application remain as filed except for the insertion of a comma in Claim 8. In a later part of the same section, pg. 2100-165, the MPEP states that "[a] specification may describe an actual reduction to practice by showing that the inventor constructed an embodiment or performed a process that met all the limitations of the claim and determined that the invention would work for its intended purpose."

Applicants respectfully submit that the term "a bFGF-active PAF antagonist" as used in the Claims is adequately described in the Specification. The term is defined in the Specification, page 7, paragraph [0030], as: "a PAF antagonist that binds to the intracellular PAF binding sites and inhibits angiogenesis otherwise stimulated by bFGF." Persons skilled in the art would clearly understand this definition based on the contents of this specification and the literature in the field. Moreover, the Specification and the Claims recite two examples of a PAF antagonist that are known in the literature to bind the intracellular PAF binding site in the literature, i.e., BN-50730 and CV3988. See Specification, page 3-4, paragraph [0007]. Additionally, the specification describes an actual reduction of practice of an embodiment that indicates the invention as claimed will work. For example, the experiments described in the examples show that two different tumor types are reduced *in vivo* using BN-50730 (e.g., Example 2, paragraphs [0048]-

[0052]), and that BN-50730 inhibits angiogenesis stimulated by bFGF, and not other growth factors (e.g., Example 6, paragraphs [0058]-[0060]). Given these explicit examples and given the teaching of the Specification of a whole, Applicants respectfully submit that the application contains sufficient written description to support the Claims as written.

Applicants respectfully submit that this rejection should be withdrawn.

Claims 1-8.

Claims 1-8 were rejected under 35 U.S.C. §112, first paragraph, for not being enabling for inhibiting any tumors beyond carcinoma of the lung and prostate.

The MPEP §2164.01(b) (pg. 2100-180) states that "[a]s long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied."

Claim 1, the only independent claim, is NOT directed to any tumor, but specifically to tumors "wherein the *growth of the tumor depends on basic fibroblast growth factor-stimulated angiogenesis*." The instant application describes the novel finding that the bFGF angiogenic pathway involves PAF and can be inhibited by PAF antagonists that bind to intracellular PAF binding sites and inhibit angiogenesis stimulated by bFGF. See, for example, Specification, paragraphs [0010] and [0029]. The term "bFGF-active PAF antagonist" is specifically defined, as shown above, as "a PAF antagonist that binds to the intracellular PAF binding sites and inhibits angiogenesis otherwise stimulated by bFGF." Applicants respectfully submit that Claim 1 is not overly broad based on the description of the technology in the Specification. Two different human tumor types were shown to be affected by the bFGF-active PAF antagonist, BN-50730, in Example 2, paragraphs [0048]-[0052]. Moreover, the Specification includes explicit experimental protocols for prospective experiments on other tumor types. See, Specification, paragraph [0052] (based on protocol described in Examples 1 and 2), and Example 9, paragraphs [0065]-[0066].

If the factors of enablement are considered, Applicants submit that the Specification as written fully enables a person skilled in the art to make and use the invention.

(1) The nature of the invention: The invention as claimed in Claim 1 is directed to:

> A method of inhibiting the growth of a tumor in a mammal, wherein the growth of the tumor depends on basic fibroblast growth factor-stimulated angiogenesis, said method comprising administering to the mammal a therapeutically effective amount of a bFGF-active PAF antagonist.

Applicants were the first to report that a PAF antagonist caused a significant reduction in angiogenesis and tumor growth in tumor models which stimulate angiogenesis using bFGF. Claim 1 does not include ANY tumor but only tumors whose growth depends on bFGF-stimulated angiogenesis. In addition, Claim 1 does not include ANY PAF antagonist but only those that fit the definition of a "bFGF-active PAF antagonist." The Specification discloses an explicit experiment to show decrease in tumor size in two separate human tumor types (lung carcinoma and prostate carcinoma) due to a bFGF-active PAF antagonist (Example 2). Moreover, using human HUVEC cells, Example 6 (paragraphs [0058]-[0060]), applicants demonstrated that the angiogenesis was inhibited by the PAF antagonist BN-50730 when stimulated by bFGF, but not by other tested growth factors.

(2) The state of the prior art: As described in the Specification, for example, paragraphs [0008] and [0029], the prior art had reported that bFGF-stimulated angiogenesis was PAF independent, in contrast to the findings by applicants. Applicants were the first to report that a PAF antagonist caused a significant reduction in angiogenesis and tumor growth in tumor models which stimulate angiogenesis using bFGF.

(3) As indicated by the Office, the relative skill of those in the art is high.

(4) The predictability or unpredictability of the art. Applicants respectfully submit that this invention as described in Claim 1 is not unpredictable. The tumor is defined as one whose growth "depends on basic fibroblast growth factor stimulated angiogenesis," and the therapeutic agent is defined as "a bFGF-active PAF antagonist," which is further defined in the Specification as a "PAF antagonist that binds to the intracellular PAF binding sites and inhibits angiogenesis otherwise stimulated by bFGF." Thus Claim 1 is not overly broad and unpredictable.

(5) The breadth of the claims: Claim 1, the only independent claim, is the broadest claim. As described above, Claim 1 does not include ANY tumor and the bFGF-active PAF antagonist is defined and described in the Specification.

(6) The amount of direction and guidance: The Specification has numerous examples that would guide a person skilled in the art on the use of this technology. For example, Example 2 describes the use of nude mice injected with human tumor cells in an *in vivo* experiment showing the treatment and subsequent decrease in tumor growth when the bFGF-active PAF antagonist was given to the mice. Example 9 describes the use of prospective experiments using nude mice to indicate that other tumors that depend on bFGF-stimulated angiogenesis to growth would also be decreased by application of the bFGF-active PAF antagonist. Given the high level of skill in the art, Applicants respectfully submit that the direction and guidance in the application is more than adequate to enable a person skilled in the art to make and use this invention.

(7) The presence of working examples: As described above, Applicants respectfully submit that the Specification contains sufficient working examples to enable Claim 1 as written, for example, Examples 2 and 9.

(8) The quantity of experimentation necessary: The experimentation necessary is merely routine given the guidance of the present Specification and using techniques known in the field. For instance, the use of nude mice and tumor cell lines are well known in the field. As described above, and particularly in Examples 2 and 9, the Specification contains the required amount of guidance. Applicants disagree that undue experimentation would be required given the skill in the art and current technology.

Thus the broadest Claim 1 is fully enabled by the current Specification, and all other claims depend from Claim 1. Applicants respectfully submit that claims 2-7 are also enabled for the above reasons, and that this rejection should be withdrawn.

Th §102 and §103 Rejections

Claims 1-4 and 6-10 were rejected under 35 U.S.C. §102(a) as being anticipated by Hunt *et al.*, particularly pages 1, 2, 5, and 8. The same reference (and designated pages) was used to reject Claims 1-10 under 35 U.S.C. §103. Applicants respectfully submit that this manuscript was submitted to a journal on September 27, 2000, but was never published. Submission of a manuscript to a journal is not a printed publication since such manuscript is not available to the general public. As noted in the MPEP §2128.02, the date a reference is accessible by the public is the operative date for use as prior art. In this case, the unpublished manuscript was never accessible by the public, and thus cannot be considered prior art for this application. Additionally, MPEP §706.02(a) states that "[a] magazine is effective as a printed publication under 35 U.S.C. 102(b) as of the date it reached the addressee and not the date it was placed in the mail." In the current case, the manuscript was never published in the journal, never reached the public, and thus cannot be a prior art reference.

Applicants respectfully submit that these rejections based on §102 and §103 should be withdrawn.

Ownership

This application is co-owned by the Board of Supervisors of Louisiana State University and Agricultural and Mechanical College ("LSU") and the Universidad de Alcalá of Madrid, Spain. Inventors J.D. Hunt, H.E. Bazan, V.L. Marcheselli, and N.G. Bazan have assigned their rights to LSU in a recorded assignment (Reel/frame 013042/0928). Inventor J.A. Builla Gomez will assign his rights to the Universidad de Alcalá. All inventors are joint inventors of Claims 1-10.

Conclusion

If any issues arise that may present an obstacle to allowance, the undersigned would welcome a telephone call to discuss such matters before further action is taken. Otherwise, allowance of Claims 1-10 at an early date is respectfully requested.

Respectfully submitted,

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December 17, 2003